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Highlights

- HME can be exploited in a broad range of applications for advanced drug delivery
- Unique advantages to be utilised in a solvent free manufacturing platform
- A means to explore the potential of continuous manufacture of pharmaceuticals
- Scale-up issue considerations, from an FDA compliance point of view
- HME regulatory guidelines for the manufacture of novel drug delivery systems

Continuous manufacturing via hot-melt extrusion and scale up: regulatory matters

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Keywords: continuous manufacturing; scale up; quality by design; PAT; FDA; hot melt extrusion.

Teaser: A solvent-free and easy to scale up HME can be implemented for continuous manufacturing of pharmaceuticals complying with the regulatory matters. HME is highly encouraged by a quality by design (QbD) viewpoint steered by the FDA.

Author biographies

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Ali Nokhodchi is a professor of pharmaceutics and drug delivery at the University of Sussex. He has supervised over 120 Mpharm, PharmD, and MSc students and 15 PhD postgraduate students at several institutions in various fields of pharmaceutical formulations and drug delivery. He is an editorial board member of over 20 peer-reviewed international journals. Ali has published over 185 research articles in various fields of pharmaceutics, including tableting, particle engineering, inhalation, nanoparticles, dissolution, skin delivery, and controlled-release formulations. In addition, he has published five book chapters on skin, controlled-release formulations, particle engineering, and inhalation products. Ali has also been the editor of a book on pulmonary delivery published by Wiley in 2015. He has been the recipient of several prizes in pharmaceutical sciences and has been listed by Essential Science Indicators in the top 1% scientists in the field of pharmacology and toxicology.

Currently, because globalization, the pharmaceutical industry is facing enormous challenges to comply with regulatory matters. Reduced patent life and overall decreased profitability of newly discovered drugs are also forcing the pharmaceutical industry to shorten the drug development time with maximum throughput. Therefore, continuous manufacturing (CM) processes via hot melt extrusion (HME) can be a promising alternative for achieving these goals. HME offers solvent-free green technology with a process that is easy to scale up. Moreover, CM provides better product quality assurance compared with batch processes, with fewer labor costs and shorter time to development. In this review, we primarily focus on various aspects of CM and the emerging application of HME to bridge the current manufacturing gap in pharmaceutical sphere.

Introduction

Over recent decades, HME techniques have appeared as an innovative manufacturing platform for various pharmaceutical applications. HME has been successfully applied to develop multiple drug delivery systems for various applications (e.g., solubility enhancement, sustained release, taste masking, implants and films and/or strips) since the early 1970s [1–5]. HME-based applications for pharmaceutical manufacturing date back to 1930s where HME was started mainly for its commercial exploitation in the plastics [6,7] and food industry [8,9]. HME has emerged as a complementary pharmaceutical manufacturing technology to develop solid dispersions of challenging drug candidates to enhance their physicochemical properties [1]. In addition, it offers a solvent-free process with fewer production steps compared with conventional methods (e.g., spray drying or freeze drying) and is easy to scale-up [10–14]. The single-unit mechanochemical approach of HME has displayed the potential to enhance the stability of thermosensitive or thermally unstable therapeutics, such as amino acids or proteins. HME also offers easy instrumentation, models, and formulae for commercial-scale manufacturing. HME can successfully be utilisized as an effective means to manufacture, optimize, and deliver various novel macromolecules and biologics. Its use has been greatly encouraged by a quality-by-design (QbD) viewpoint steered by the US Food and Drug Administrations (FDA). In this review, we primarily focus on the foregoing subject areas.

Continuous manufacturing

The term 'CM' in pharmaceutical industry refers to a process whereby pharmaceutical materials (e.g., final dosage forms) are manufactured continuously without any process interruptions for intermediate processing steps [15]. In batch manufacturing, all materials are generally manufactured in unit operations segmented in a long process that is lengthy and cost intensive [15–20]. In batch manufacturing, the product is most frequently tested off-line after processing is complete; thus, there is a lack of opportunity for real-time monitoring during the operational process. Therefore, the industry is being encouraged to switch to CM, which has numerous benefits, such as integrated processing with fewer steps (no manual handling, increased safety, and shorter processing times). In addition, other factors, such as smaller equipment and facilities, more flexible operation, lower capital costs, and rapid development screening over many conditions, are important for the adaptation of CM for pharmaceutical manufacturing. CM also provides scope for extended on-line monitoring for product quality assurance in real time [15–24]. During the industrial production of drugs, active substances rarely have the physical requirements needed for processing and manufacturing the final products and, therefore, the potential of functional excipients has been revolutionizing the pharmaceutical industry.

CM and HME processing technology

Since its introduction during the late 1970s, HME has been utilized successfully in manufacturing pharmaceutical products for multiple drug delivery strategies [1–9,25–28]. HME can be adopted as a CM platform by optimizing a suitable set of instrumentations (Figure 1). HME is operational with single-screw or twin-screw instruments. Generally, a single-screw extruder has a single screw with conveying properties built as close to the barrel as possible to produce sufficient shear [1–3]. By contrast, a twin-screw extruder (TSE) can be adapted to various screw designs and configurations as per the required optimization of the formulations and the final dosage forms. Screw geometry of the twin screw (co-rotating or counter-rotating) produces the highest shear and offers excellent mixing capacity in the barrel. The main advantages of HME techniques include its viability for continuous processing without the use of solvents and the fact that it is economically friendly and easy to scale up [1,2].

A new terminology known as 'Quality by Design' (QbD) is now being promoted by the regulatory authorities and is largely described in the International Conference of Harmonization (ICH) guidelines, particularly in paragraphs such as ICH Q2 (R2), ICH Q9, and ICH 10 [19]. These paragraphs in the ICH guidelines describe QbD as approaches that focus on science-based design and subsequently lead to manufacturing processes. In a QbD approach, predefined product quality attributes are used to develop a model design space [24]. Process analytical technology (PAT) initiated by the FDA is used for the in-line monitoring of critical product parameters (attributes) linked to the product quality. PAT is normally used to monitor and study the formulation development and manufacturing steps [24]. Near-infrared (NIR), Raman, and ultrasound spectroscopy are a few examples of the most commonly exploited techniques across the pharmaceutical and food industries and are suitable for an increased number of PAT applications [29].

In recent years, there has increasing interest within the pharmaceutical industry in the use of CM processes for pharmaceutical product manufacture, design, and optimization [30]. In reality, the conventional batch processes of manufacturing have several drawbacks (e.g., poor controllability, low yield, and difficult scalability) and are labor intensive [31,32]. Thus, ongoing efforts have focused on the development and optimization of continuous processes. However, in the pharmaceutical industry, the application of CM, automation, and control is still a challenging task. Therefore, there is an immense need to overcome the challenges involved in CM before the design and successful implementation of this process.

CM applications via HME

The current scenario of pharmaceutical processing in the manufacturing environment is mainly an old-fashioned batch processing where each portion of the dosage form is directed to each single lot (batch), which increases the chance of significant batch-to-batch variation. This batch manufacturing process is an established approach that has been utilized for decades to satisfy the demands of both the manufacturer and regulatory authorities. However, whereas other industries, such as the petrochemical, chemical, or food and polymer industries, have steadily moved towards using CM processes, the pharmaceutical industry has yet to fully realize the benefit of CM in terms of cost and quality considerations. A study comparing batch with continuous processing reviewed broadly the reasons for the strong link between the pharmaceutical industry and the use of batch processing [33]. The limited flexibility, and intensive costs and time taken for drug developments are the major reasons why many industries have moved to using continuous processing approaches. Other important factors governing this move include reducing the size of the manufacturing plant and using available in-house capacity for XXXX [DE1][30,31]. However, a revision of the manufacturing regulations related to the use of CM will prove it to be beneficial for patients and healthcare systems as a whole [34,35]. A recent spotlight discussion illustrated how various initiatives to implement new methodologies for quality testing and analysis are being mapped by the pharmaceutical industry and regulatory authorities [30].

Since the start of the new scientific era, pharmaceutical companies have always competed technically, with a special focus on innovation. A report recently suggested that approximately US$802 million is spent before the marketing approval of a new drug is received [17,23]. In addition, the estimated costs of drug research and development will increase the drug development expenditure pot. CM will ease this process in many ways for the

industry, enabling it to cut costs by converting processes from batch to CM along with appropriate real-time monitoring using PAT tools for the implementation of QbD.

In terms of appropriate real-time monitoring and investigations using PAT tools during a CM process such as HME, there are several approaches that have been reported in the literature to characterize residence time distributions (RTD) (which are considered an important factor for CM and scale-up) during the processing steps involved in extrusion in a manufacturing sphere [36–43]. One of the aspects of process development in a continuous mode of operation is the thorough analysis and understanding of RTD via the processing steps and descriptions of the degree of intermixing at each the processing step. Another key point to consider when designing and optimizing a CM process as well as the scale-up of HME is the implementation of the overall manufacturing throughput or feed rate. The change in the rate of the throughput and/or feed can have fundamental effects on various events inside the extruder barrel, such as shear, mixing, and heating, which normally impact the material quality and the blending for final product processing. Therefore, changes in throughput in a continuous operation of the HME process have a vital role and form an important part of the development of the overall control policy enforced by regulatory bodies.

Krier *et al.* [44] reported an investigation of the exploitation of HME processing as novel continuous pharmaceutical manufacturing process technique for the development of medical implants. In their study, the authors identified four critical quality attributes (CQAs) of the implant manufacturing process by HME [i.e., the implant diameter, the quantity of the active pharmaceutical ingredient (API), the homogeneity distribution of the API, and the thickness of the membrane]. The implant diameter and quantity of API were controlled in-line with a laser measurement, and NIR and Raman spectroscopy, respectively (Figure 2). NIR spectroscopy appeared to be an easier PAT tool to use compared with Raman spectroscopy because it was less sensitive to external changes.

Similarly, Wahl *et al. [*45] implemented CM via HME processing of vegetable calcium stearate (CaSt) and paracetamol monitored by PAT tools. In this study, the authors used in-line NIR spectroscopy to monitor and control the process by using a novel design of the die. The authors located the fiber optic probe in different sections of the barrel. The whole study was analyzed using a chemometric model implemented in SIPAT for the real-time measurement of quality attributes. The authors used the concentrations of API as critical quality attributes in the study. The bespoke in-line results were in good agreement with theoretical data. The authors concluded that the screw design was the dominant factor in determining the content uniformity of the extrudates manufactured during the study.

In another study, Muehlenfeld *et al.* [46] evaluated an extrusion process in a continuous platform to evaluate the effect of both powder and liquid feeding systems. The authors treated the powder and the liquid feed rate as crucial quality parameters. The cohesiveness and electrostatic charging were the main challenges to optimizing the system. The optimized extrusion process with a slow feed rate and the addition of a small amount of plasticizer (from 2.5% to 15% w/w) resulted in a homogenous plasticizer distribution throughout the extrudates. By contrast, in a continuous wet extrusion, larger quantities of water resulted in the spheronization of the extrudates inside the extruder barrel.

Baumgartner *et al.* [47] recently reported the conversion of an optimized stable nanosuspension into solid forms via a single-step manufacturing process involving HME. The authors named the process, which improved the solubility of a model drug (phenytoin), the 'NANEX' process. In this study, phenytoin nanosuspensions were prepared via media milling using different stabilizers. A stable nanosuspension was obtained using Tween 80 as a stabilizer. The matrix material (Soluplus) was gravimetrically fed into the hot melt extruder. The suspension was introduced through a side feeding device and mixed with the molten polymer to immediately devolatilize the water in the nanosuspension. Phenytoin nanocrystals were dispersed and embedded in the molten polymer. The authors concluded that, regardless the type of polymer, the optimized manufacturing process enhanced the solubility of the drug nanocrystals.

Similarly, Patil *et al.* [48] recently manufactured solid lipid nanoparticles (SLN) via HME using QbD principles. The continuous production of SLN was achieved by combining two different approaches of HME and high-pressure homogenization (HPH) to reduce the particle size. Fenofibrate (FBT) was incorporated into SLN using HME-HPH methods to form a model drug. Better control and the reduced size of the drug were achieved via this novel manufacturing approach compared with HME or HPH alone. The pharmacokinetic study results demonstrated a statistical increase in C_{max}, T_{max}, and $AUC_{0–24h}$ in the rate of drug absorption from SLN formulations compared with the crude drug and marketed micronized formulation.

Fonteyne *et al.* [49] studied continuous granulation by evaluating the properties of raw materials. In their research, HME was used to produce tablets from powder through a wet granulation technique in a continuous mode of operation (ConsiGma™ 25). The group also implemented an experimental design for both product and process variability assessment in terms of the granule size distribution. Kumar *et al.* [50] investigated a novel method for better understanding and simulating the residence time distribution in a twin-screw extruder/granulator (TSG). In this HME-based CM approach, the study revealed that the kneading block serves as a plug-flow zone inside the granulator, which has a pivotal role in optimizing the bespoke platform. The authors concluded that the balance between the throughput and the conveying of the materials inside the extruder barrel is important to achieve good mixing.

Vercruysse *et al.* [51] reported a study on TSG to investigate the impact of the screw configuration of a 25-mm granulator on the particle size distribution (PSD). By optimizing the process with kneading elements, the authors

found that, although the width of the PSD was partially mono-modal and narrow, a homogeneous liquid distribution was achieved throughout the process. The authors also observed a significant portion of oversized agglomerates during the granulation process. In similar study [52], the authors investigated full-scale manufacturing for a scale-up process. The authors found that the torque and the barrel wall temperature stabilized after a certain period of time because of the initial layering of the screws, which resulted in slightly deviating granule and tablet quality attributes.

Recently, Keen *et al*. [53] developed a continuous granulation process for the direct production of granules using a continuous twin-screw extrusion processing with glyceryl behenate as a binder and manufactured controlled-release tablets containing tramadol HCl (Figure 3). In this study, granules were formed by a combination immersion/distribution mechanism and were observed to contain desirable polymorphic forms of glyceryl behenate. This optimized manufacturing technology also bypassed any further micronization of the granules. The drug-release rate from the tablets was found to be stable for 3 months under accelerated conditions.

Jones *et al*. [54] determined the thermorheological properties of Eudragit E100 and hydroxypropylcellulose and their blends by implementing advanced capillary rheometry. The study was conducted either in the presence or absence of the drug. Fule *et al*. [55] reported the feasibility of industrially manufacturing co-formulated extrudates using two model drugs in hydrophilic polymeric matrices. The use of theoretical and experimental drug–polymer interaction assessment with determination of processability and structures of dispersions in two polyvinylpyrrolidone-based polymers (PVP and PVP vinyl acetate, PVPVA) was highlighted by Chan *et al.* [56]. Dong *et al.* [57] reported a novel *in situ* synchrotron wide-angle X-ray diffraction (WAXD)-based approach to rapidly and accurately screen the formation of cocrystal and/or salts during heating inside an extruder barrel. The authors concluded that a developed bespoke technique can successfully be utilized as a promising predictive tool for both salts and cocrystals.

Omar *et al*. [58] described the effect of the type and degree of amorphicity in three different lactoses on the properties of ribbon produced using roller compaction. Similarly, Al-Asady *et al*. [59] investigated different materials (microcrystalline cellulose, hydroxypropyl methylcellulose, Maltodextrin, lactose, sodium carbonate, and calcium carbonate) for nanoindentation hardness produced via a granulation approach. The influence of API hydrophobicity on continuous wet granulation was studied in a foamed twin-screw granulation by Li *et al.* [60].

Maniruzzaman *et al*. [61] described a study to manufacture free-flowing amorphous powder using inorganic excipients in a single-step manufacturing process. In a second report, the same group reported a novel case of utilizing a twin-screw granulator for the enhancement of the dissolution rate of the poorly water-soluble drug ibuprofen, as depicted in Figure 4 [62]. Similarly, a novel granulation process was exploited by Sayin *et al*. [63] by using an 11-mm twin-screw HME machine. In this study, the authors reported the in-line monitoring of the granules processed via a bespoke image analysis technique. The TSG process followed by tabletting in a continuous mode of operation were reported by Meier *et al*. [64]. Kelly *et al*. [65] designed a novel transflectance NIR probe to simultaneously measure the drug and plasticizer content of polymer melts with varying opacity during a continuous HME process. The formulation and development of sustained-release matrix tablets via a continuous twin-screw melt granulation process presented by Repka and coworkers showed that both pH-dependent and -independent polymer matrices can be used to develop sustained-release formulations [66]. In current pharmaceutical manufacturing, tablets are commercially manufactured in a continuous compaction operation [67].

Scale-up methodologies

The scale-up [40,68] of a manufacturing process is a prerequisite to ensure industrial production without compromising the quality parameters of the product. For continuous HME, scale-up for a pilot scale production can be achieved by running the process for a longer period or increasing the material feed rate and/or screw speed. In addition, increasing the barrel size and screw diameter or transferring the heat across the barrel are other ways of achieving successful scale-up in pharmaceutical manufacturing. There are some challenges involved in terms of the quality associated with each type of scale-up process; for example, increasing the throughput and/or material feed rate could severely affect the residence time and energy deviances. Similarly, increasing the barrel size without changing the feeding rate could have different effects on product quality. Moreover, changes in both the screw speed and the feed rate can increase the shear force and torque inside the barrel, stopping the process and significantly impacting both the process and product quality. Overall, despite these difficulties and challenges, the scale-up via HME processes can be optimized and undertaken by careful evaluation of the critical process parameters (CPP) during the development and validation stages.

Scale-up consideration is key to implementing a successful scale-up process in CM via HME. Scale-up from a mid-size to a larger size TSE is more predictable and the intense mixing that is normally achieved via extrusion processing is more repeatable than is batch mixing. This is because a typical TSE benefits from a shorter mass transfer, which is inherent in its design. The successful design of the scale-up study in HME processing is dependent on managing several parameters, such as the residence time distribution using screw design, screw speed (rpm), and degree of screw fill. This should be coupled with a thorough understanding of the boundary conditions and process parameters and how these parameters in the event of a small size extrusion batch on a smaller scale can be translated in terms of the quality attributes of the product.

Technically, in a successful scale-up, the fundamental geometry of the bench top extruder has to match that of the larger extruder. In this context, the ratio of the outer and inner diameter of the screw is considered a key

parameter. The screw elements of an extruder (TSE) comprise mainly two types of screw block: (i) conveying blocks; and (ii) mixing blocks. The first set of blocks is used to convey the materials through the barrel, whereas the mixing blocks perform intense mixing of the extrudates inside the barrel. Generally, in a typical TSE, two types of mixing are observed: dispersive mixing and distributive mixing. Moreover, screws used in a TSE are modular and can be easily changed to optimize the screw profile. In a scale-up process, the screw profile should be kept similar between the small TSE and the large TSE. Mass or heat-transfer limitations can arise at larger scales, thereby affecting dispersion, distribution, and resulting product uniformity. In addition, with the increase in screw diameter, the tip speed of the rotating screw flights increases, thereby raising the peak shear to which the material is exposed. The effects of high peak shear can be reduced with tight acceptance windows and specialized mixing element designs, which potentially improve the self-wiping characteristics of a TSE.

Design-of-experiment (DoE) approaches alongside process models can be useful for defining and predicting the process-based design space. In addition, software can be used to predict and determine optimum scale-up conditions, although the availability of such software is still questionable. The main reason for this is the requirement of raw-material data, which can not only be difficult to calculate, but also unfeasible in some cases. In TSE processing, the mixture of components changes as it moves through the heated barrel under controlled conditions and converts from a solid to a nonNewtonian fluid. Research endeavors to develop a robust software tool are ongoing and this could result in a complete software solution in the near future. Despite the innovative software revolution in scale-up via TSE instruments, skilled personnel remain key to successful scale-up implementation in the real world.

Feeders (via which materials are fed into the extruder) are considered upstream processing equipment, should be considered during scale-up. In the current pharmaceutical extrusion paradigm, two types of feeding process are adopted: (i) split feeding (the polymeric excipient and the API are fed separately into the extruder); and (ii) premix feeding [a premix of the starting materials (polymer/carriers and API) are performed in a dry blend and subsequently fed to the extruder in one stream].

In the commercial extrusion sphere, the two types of feeding process are frequently used, although it depends on the applications as well as the physical forms of the feeding materials. The split feeding process is a must in the event of feeding different physical forms (e.g., if the excipient is in the form of pellets and the API a fine powder). Given that premixing performs a high percentage of the mixing before extrusion, it still outperforms split feeding in terms of the intense mixing, because, in a split-fed system, the extruder does 100% of the mixing. The latter can lead to decreased rates or less mixing of the excipients with API. By contrast, a split feeding system might be the only resort for processing API that is thermosensitive, requiring the feeding to happen somewhere in the middle of the extruder barrel after the excipient is at least partly melted. In laboratories, premix is still preferred to split-feeding because small volumes (which are common in lab settings) require specialized feeding equipment to meter and estimate the feeding accurately. Therefore, matching the feeding method during a successful scale-up is important because the feeding method significantly affects mixing and, thus, the quality attributes of the products. Similar to the up-stream equipment, downstream processes, such as cooling, pelletizing, and micronizing, should be considered as part of the scale-up, although these are frequently neglected in development timelines. The inconsistency or incompleteness of the process during downstream processing can lead to a tailback in the overall manufacturing process.

Scale-up models and formulas in HME

In general terms, scale-up is required to optimize large-scale manufacturing without compromising the quality parameters of the product. A thorough investigation of the scale-up processes in CM platforms using HME can be optimized using several models and theories. Various case studies have been reported using a adiabatic melt extrusion process derived from the cubic law [69]. Similarly, a square law can also be suggested based on the heat transfer when considering a successful scale-up [70]. Nevertheless, the balance can deviate based on the geometric similarity and the melt temperature because they might not be constant throughout the scale-up. A more advanced adiabatic index has also been proposed and developed aimed at keeping the melt temperature constant [70,71]. As described below, there are other technical formulas and models that have a vital role in the successful scale-up via HME processing technology.

Generally, in a TSE system, shear forces result in mixing and, thus, the shear rate determines the velocity gradient between two surfaces moving at different speeds. In a typical TSE, the shear rate is calculated as a function of screw outside diameter, overflight gap, and the screw speed, as shown by Equation 1:

$$Shear\ rate = \frac{\pi * D * n}{h} \quad [1\ ],$$

where, D is the screw diameter, n is the screw speed in rpm, and h is the overflight clearance.

Shear stress is often referred to as the magnitude of the applied stress inside the barrel that the conveying materials experience and is expressed by Equation 2 as a function of the shear rate and viscosity.

$$Shear\ stress = Ec * Shear\ rate \quad [2],$$

where Ec is the viscosity. Barrel temperatures have a key role in controlling the viscosity of the melt inside a barrel. Low or high viscosity impacts the mixing quality (e.g., high viscosity facilitates dispersive mixing).

Specific mechanical energy (SME) measures the total mechanical energy (as a form of heat) put into the extrudate during high shear mixing. Specific mechanical energy consumption (SMEC) represents the energy entering the extrusion system per unit mass through viscous dissipation. As shown by

Equation 3, the SMEC depends on the torque, rotation of the screw, and the feed rate or throughput, and is measured in kJ/kg.

$SMEC = \frac{\tau * n}{\omega}$ [3],

where τ is torque (Nm), ω is feed rate (kg/h), and n is screw speed (rpm).

In general terms, at a constant feed rate, the higher the torque and screw speed, the higher the shear inside the barrel and, thus, the SMEC, which could have a significant impact on the overall force inside the barrel, resulting in a significant increase in pressure. It has been found that, with the increase in screw speed from 50 rpm to 400 rpm (temperature constant) during a scale-up, the torque increased from 8.8 Nm to 12.7 Nm, impacting the resultant SMEC values, which exhibited a significant effect on the state of the extrudates [72]. Similarly, the increasing screw speed favored intense mixing inside the barrel by increasing the pressure (8 bars) and the torque (12.7 Nm). It was claimed that the increased screw speed is directly proportional to the increase in both the torque and the pressure (Equation 3).

$$SMEC = \frac{\tau * n}{\omega} \quad (3)$$

Residence time distribution is highly dependent upon the degree of screw fill. Equation 4 is used to determine the residence time;

$RT(s) =$ [illegible] [4],

where RT is residence time in seconds, SV is specific volume, SG is specific gravity, L/D is the L/D extruder ratio, % fill is the degree of fill expressed as a decimal (i.e.,, 40% = 0.4), and Q is the throughput expressed in kg/h.

Volumetric scale-up in the CM of pharmaceutical products using HME processes is applied to maintain the same degree of fill and the same RTD. For geometrically similar extruders with different diameters, the final feed rate in a twin-screw extruder is assessed using Equation 5 [71]:

$$Q_T = Q_M \times \frac{D_T^3}{D_M} \times \frac{N_T}{N_M} \quad (5)$$ [DE2],

where Q_T and Q_M are the final and initial process feed rate, respectively; D_T and D_M are the screw diameters after and before scale-up, respectively; and N_T and N_M are the screw speed after and before scale-up, respectively. In simplified conditions, if volumetric scale-up is conducted using similar geometric extruders (e.g., 11-mm or 16-mm twin-screw extruder from ThermoFisher, Germany) and the screw speed is kept constant, the process throughput is expected to obey the cubic law.

Scale-up of the CM of pharmaceuticals using HME processes can be assessed by optimizing the heat transfer of the barrel, where the scale-up of the manufacturing will entirely dependent on the heat transfer. In this method, the surface area for heat transfer is taken to be equivalent to the barrel surface area. Based on this, the process throughput will be scaled up while maintaining the heat transfer rate, as shown by Equation 6 [71]:

$$Q_T = Q_M \times \frac{D_T^2}{D_M^2} \times \frac{N_T}{N_M} \quad (6)$$ [DE3]

where Q_T and Q_M are the targeted and initial process throughput, respectively; D_T and D_M are the targeted and initial screw diameter, respectively; and N_T and N_M are the screw speed after and before scaling up, respectively. From this, it can be found that the heat transfer scale-up follows the square law if the screw speed does not change.

The specific torque and specific energy (SE) input is considered a critical parameter in the production of high-energy compositions, including amorphous systems. Therefore, successful scale-up of a CM process via HME depends to a large extent on the steady constant level of SE input. Generally, the mechanical energy input in an HME process during the optimization of scale-up methods, is calculated and determined by using Equation 7:

$$E = E_{max} \times \frac{N}{N_{max}} \times \frac{\tau}{\tau_{max}} \times Gearbox\ Rating \quad (7)$$ [DE4],

where E_{max}, N_{max}, and τ_{max} of an extruder are usually predetermined by the instrument design. The exact value of maximum torque and screw speed is measured directly from Equation 7 [71].

Scale-up applications via HME

Gryczke *et al.* recently investigated the influence of process parameters on the RTD of the material within the extruder and the SMEC during the extrusion process when Soluplus® was used as the standard carrier matrix [73]. The authors also determined the possibilities of scaling up the process from a lab scale to a production line scale for industrial manufacturing. To save development time and material, the predictability of the scale-up step was determined with a design of experiments (DoE) approach, as described below

Soluplus® was extruded using three different sizes of co-rotating TSEs manufactured by ThermoFisher (Germany), in different process settings following a DoE plan. As important process parameters, the RTD was measured with a tracer in each set-up and the SMEC was calculated. In addition to these process parameters, all standard parameters (e.g., temperature of the melt at the extruder die, the pressure at the die and torque) were also measured. From the RTD, the mean residence time (MRTD) was calculated. RTD was obtained by measuring the concentration of a color pigment with a photometric and a colorimetric method.

The authors analyzed the data of the three independent DoE via ANOVA and the resulting multidimensional regression models were used to calculate the design spaces, which were compared for their overlap between the different scales of the extruders. It was observed that, with increasing barrel temperatures, the SMEC decrease. In fact, with increasing barrel temperature, the viscosity of the material decreases, followed by a decreased torque (as per Equation 3). The authors concluded that, with an increasing feed rate and increasing volume-specific feed load (VSFL), the mechanical energy input decreased, because more portions of the material would share the mechanical energy supplied by the system (Figure 5).

A scale-up investigation was performed involving a stable, solid dispersion of Eudragit EPO/nifedipine and Eudragit NE 30 D formulation. The manufactured and scaled-up solid dispersions were examined with different drug loadings. Polymers were extruded and granules were obtained via a micronization process at a downstream stage. Scale-up parameters were calculated with software and the screw speed was set to 140 rpm; this was subsequently balanced on the mass throughput for a 27-mm extruder and calculated to be 100 rpm [74].

Although scale-up studies via HME processes in the plastics industry is designed for high-throughput products up to 50 tons/h, the laboratory scale in pharmaceutical and/or plastic research is related to extruder sizes of approximately 30 mm in screw diameter, which translates into feed rates of approximately 4–6 kg/h [75–78]. Recently, Zeceivic *et al*. reported a numeric process simulation-based scale-up study via HME processing using process data as well as rheological and thermal properties of the formulations. The scale-up optimized in a 16-mm and 18-mm TSE confirmed and refined the simulation model. The authors concluded that the scale-up investigation was an efficient and reliable procedure to identify and manufacture solid dispersions via HME from a micro- to pilot-scale [79]. Similarly, a high shear dry granulation was developed and scaled up to a 10-kg batch size [80].

Regulatory aspects

The 'batch' is defined by the FDA (21 CFR 210.3) as, 'A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture' [81,82]. By contrast, in the same guidelines, a 'lot' is defined as 'a batch, or a specific identified portion of a batch, that has uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits'. By definition, the 'batch' is of 'uniform character and quality within specified limits', which necessitates the regulatory expectation for implementing a CM platform [82]. This interpretation by itself will assist and motivate the pharmaceutical industry to evolve towards CM, which is technically a single-step manufacturing process.

The FDA has also issued a draft guidance called *PAT–A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance* (Table 1 and Figure 6) [81,82]. The main objectives of this guidance are to describe a regulatory agenda to increase the amount and level of groundbreaking pharmaceutical manufacturing knowledge. The draft guidance [82] states: 'Process Analytical Technology, or PAT, should help manufacturers develop and implement new efficient tools for use during pharmaceutical development, manufacturing, and quality assurance while maintaining or improving the current level of product quality assurance'. The guidance is regarded as the center around the concept. The draft regulation also [82] positions, 'facilitating continuous processing to improve efficiency and manage variability'. Therefore, these regulatory statements will further encourage pharmaceutical industries to evolve from frozen batch manufacturing to begin to realize the tremendous benefits of CM processes. Similar to the FDA, regulatory authorities across the globe are emphasizing the adoption of CM processes. These concepts are highlighted in the ICH guidelines, especially in Q8 (R2), Q9, Q10, and Q11 [83–86]. Similarly, the concept of CM has also been highlighted by the QbD terminology issued by the FDA. While describing the principles of QbD, the ICH recommend a 'greater understanding of the product and its manufacturing process' to 'create a basis for more flexible regulatory approaches' [87], with a focus on the systematic understanding of a control strategy, 'derived from current product and process understanding that assures process performance and product quality'. The guideline confirms that 'the degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations'. There is a clear indication that all of the above-mentioned guidelines and the recently emphasized QbD framework could have a significant impact on the development, optimization, and implementation of HME processing [88] as a CM process.

Concluding remarks

From a macroscopic viewpoint, it would be possible to develop and implement a fully continuous HME process in a pharmaceutical setting. The correct implementation of a CM process would reduce variation associated with product quality attributes and processing parameters. Thus, the ability to maintain parameters and processing conditions could be key to achieving operational benefits for CM via an emerging manufacturing platform (e.g., HME) and the subsequent scale-up for commercial exploitation. Recent guidelines from the regulatory authorities clearly envision an upcoming revolution in CM processes to replace the current batch manufacturing approach.

References[DE5]

1 Maniruzzaman, M. *et al.* (2013) Drug-polymer intermolecular interactions in hot-melt extruded solid dispersions. *Int. J. Pharm.* 443, 199–208

2 Maniruzzaman, M. *et al.* (2013) Dissolution enhancement of poorly water-soluble APIs processed by hot-melt extrusion using hydrophilic copolymers. *Drug Dev. Ind. Pharm.* 39, 218–227

3 Maniruzzaman, M. *et al.* (2012) Taste masking of paracetamol by hot-melt extrusion: an *in vitro* and *in vivo* evaluation. *Eur. J. Pharm. Biopharm.* 80, 433–442

4 Grycze, A. *et al.* (2011) Development and evaluation of orally disintegrating tablets (ODTs) containing ibuprofen granules prepared by hot melt extrusion. *Colloids Surf. B Bioint.* 86, 275–284

5 Vithani, K. *et al.* (2013) Sustained release solid lipid matrices processed by hot-melt extrusion (HME). *Colloids Surf. B Biointerfaces* 110, 403–410

6 Cannon, *et al.* (2010) Safety of anacetrapib in patients with or at high risk for coronary heart disease. *New Engl. J. Med.* 363, 2406–2415

7 Breitenbach, J. (2006) Melt extrusion can bring new benefits to HIV therapy. *Am. J. Drug Deliv.* 4, 61–64

8 Crowley, C.M. *et al.* (2007) Pharmaceutical applications of hot-melt extrusion: Part I. *Drug Dev. Industrial Pharm.* 33, 909–926

9 Maniruzzaman, M. *et al.* (2012) *Hot-Melt Extrusion (HME): From Process to Pharmaceutical Applications*, INTECH Open Access Publisher

10 Repka, M.A. *et al.* (2012) Melt extrusion: process to product. *Expert Opin. Drug Deliv.* 9, 105–125

11 Repka, M.A. *et al.* (2008) Applications of hot-melt extrusion for drug delivery. *Expert Opin. Drug Deliv.* 5, 1357–1376

12 Repka, M.A. *et al.* (2007) Pharmaceutical applications of hot-melt extrusion: Part II. *Drug Dev. Ind. Pharm.* 33, 1043–1057

13 Lang, B. *et al.* (2014) Hot-melt extrusion – basic principles and pharmaceutical applications. *Drug Dev. Ind. Pharm.* 40, 1133–1155

14 Repka, M.A. *et al.* Melt extrusion: process to product. *Expert Opin. Drug Deliv.* 9, 105–25

15 Rawendaal, C. (2001) *Polymer Extrusion* (4th edn), Hanser Publications

16 Guy, R. (2001) *Extrusion Cooking - Technologies and Applications*, Woodhead Publishing

17 Bryn, S. *et al.* (2015) Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. May 20–21, 2014 Continuous Manufacturing Symposium. *J. Pharm. Sci.* 104, 792–802

18 Hurter, P. *et al.* (2013) Article title. *AAPS Newsmag. Manufact. Sci. Eng.* 16, 14–19[DE6]

19 Anon. (2009) *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Pharmaceutical Development Q8 (R2)*, ICH

20 Zhang, X.M. et al. (2008) Article title[DE7]. *Polymer Eng. Sci.* 48, 19–28

21 Kossik, J. (2002) Think small: pharmaceutical facility could boost capacity and slash costs by trading in certain batch operations for continuous versions. *Pharma. Manufact.* October 18[DE8]

22 Abboud, L. and Hensley S. (2003) Factory shift: new prescription for drug makers: update the plants. Wall Street J. September 3

23 Dimasi, J. *et al.* (2003) The price of innovation: new estimates of drug development costs. *J. Health Econ.* 22, 151–185

24 Islam, M.T. *et al.* (2014) Development of sustained-release formulations processed by hot-melt extrusion by using a quality-by-design approach. *Drug Deliv. Translat. Res.* 4, 377–387

25 Moradiya, H.G. *et al.* (2014) Cocrystallisation of Carbamazepine and trans-cinnamic acid via melt extrusion process. *CrysEng Comm.* 16, 3573–3583

26 Maniruzzaman, M. *et al.* (2014) Prediction of polymorphic transformation of paracetamol in solid dispersions. *J. Pharm. Sci.* 103, 1819–1828

27 Maniruzzaman, M. *et al.* (2015) Molecular modelling as a predictive tool for the development of solid dispersions. *Mol. Pharm.* 12, 1040–1049

28 Maniruzzaman, M. and Douroumis, D. (2015) Continuous manufacturing and process analytical tools. *Int. J. Pharm.* 496, 1–2

29 Maniruzzaman, M. *et al.* (2012) A review of hot-melt extrusion (HME): process technology to pharmaceutical products. *ISRN Pharm.* 2012, 436–763

30 Todd, D.B. (1975) Residence time distribution in twin-screw extruders. *Polym. Eng. Sci.* 15, 437–443

31 Ganjyal, G. and Hanna, M. (2002) A review on residence time distribution (RTD) in food extruders and study on the potential of neural networks in RTD modeling. *J. Food Sci.* 67, 1996–2002

32 Reitz, E. *et al.* (2013) Residence time modeling of hot melt extrusion processes. *Eur. J. Pharm. Biopharm.* 85, 1200–1205

33 Kossik, J. (2002) Think small: pharmaceutical facility could boost capacity and slash costs by trading in certain batch operations for continuous versions. *Pharma. Manufact.* October 18[DE9]

34 Dimasi, J. *et al.* (2003) The price of innovation: new estimates of drug development costs. *J. Health Econ.* 22, 151–185[DE10]

35 Proctor, L. (2002) High pressure asymmetric hydrogenation as part of a two stage continuous process for the commercial manufacture of statin intermediates. In *Proceedings of the 5th International Conference on Scale-Up of Chemical Processes, September 2002* (eds), pp. 19–38, Publishers[DE11]

36 Proctor, L.D. and Warr, A.J. (2002) Development of a continuous process for the industrial generation of diazomethane. *Org. Proc. Res. Dev.* 6, 884–892

37 Meyer, T. (2002) Scale up of polymerization processes: a practical example. In *Proceedings of the 5th International Conference on Scale-Up of Chemical Processes, September 2002* (eds), pp. 128–159, Publishers[DE12]

38 Anderson, N.G. (2001) Practical use of continuous processing in developing and scaling up laboratory processes. *Org. Proc. Res. Dev.* 5, 613–621

39 Rouni, A.M. (2002) Intensification to accelerate. Fine chemicals producers may have a way out of the inefficiencies of batch processing. *Chem. Eng. News* 80, 36–37

40 Mollan M. (2003) Historical overview. In *Pharmaceutical Extrusion Technology* (Ghebre-Sellassie, I. and Martin, C.E., eds), pp. 1–16, CRC Press

41 Todd, D.B. (1998) Introduction in Plastics Compounding Equipment and Processing, Publisher[DE13]

42 Wagner, J. and Vlachopolous, J., eds (2001) *The SPE Guide on Extrusion Technology and Troubleshooting*, Society of Plastics Engineers

43 Nowak, S. (2008) Feeders in milling and micronization of pharmaceutical powders. *Chem. Info[DE14]*

44 Krier, F. *et al.* (2013) PAT tools for the control of co-extrusion implants manufacturing process. *Int. J. Pharm.* 458, 15–24

45 Wahl, P.R. *et al.* (2013) Inline monitoring and a PAT strategy for pharmaceutical hot melt extrusion. *Int. J. Pharm.* 455, 159–68

46 Muehlenfeld, C. and Thommes, M. (2014) Small-scale twin-screw extrusion – evaluation of continuous split feeding. *J. Pharmacy Pharma.* 66, 1667–1676

47 Baumgartner, R.A. *et al.* (2014) Nano-extrusion: a promising tool for continuous manufacturing of solid nano-formulations. *Int. J. Pharm.* 477, 1–11

48 Patil, H. *et al.* (2015) Continuous production of fenofibrate solid lipid nanoparticles by hot-melt extrusion technology: a systematic study based on a quality by design approach. *AAPS J.* 17, 194–205

49 Fonteyne, M. *et al.* (2015) Impact of microcrystalline cellulose material attributes: a case study on continuous twin screw granulation. *Int. J. Pharma.* 478, 705–717

50 Kumar, A. *et al.* (2015) Ingmar NopensConceptual framework for model-based analysis of residence time distribution in twin–screw granulation. *Eur. J. Pharm. Sci.* 71, 25–34

51 Vercruysse, J. *et al.* (2015) Impact of screw configuration on the particle size distribution of granules produced by twin screw granulation. *Int. J. Pharm.* 479, 171–180

52 Vercruysse, J. *et al.* (2015) Use of a continuous twin screw granulation and drying system during formulation development and process optimization. *Eur. J. Pharm. Biopharm.* 89, 239–247

53 Keen, J.M. *et al.* (2015) Continuous twin screw melt granulation of glyceryl behenate: development of controlled release tramadol hydrochloride tablets for improved safety. *Int. J. Pharm.* 487, 72–80

54 Jones, D.S. *et al.* (2015) Characterisation and modelling of the thermorheological properties of pharmaceutical polymers and their blends using capillary rheometry: implications for hot melt processing of dosage forms. *Int. J. Pharm.* 496, 86–96

55 Fule, R. *et al.* (2015) Development of hot melt co-formulated antimalarial solid dispersion system in fixed dose form (ARLUMELT): evaluating amorphous state and *in vivo* performance. *Int. J. Pharm.* 496, 137–156

56 Chan, S-Y. *et al.* (2015) An investigation into the influence of drug–polymer interactions on the miscibility, processability and structure of polyvinylpyrrolidone-based hot melt extrusion formulations. *Int. J. Pharm.* 496, 95–106

57 Dong, P. *et al.* (2015) In-situ synchrotron wide-angle X-ray diffraction as a rapid method for cocrystal/salt screening. *Int. J. Pharm.* 496, 107–116

58 Omar, C.S. *et al.* (2015) Roller compaction: effect of morphology and amorphous content of lactose powder on product quality. *Int. J. Pharm.* 496, 63–74

59 Al-Asady, R.B. *et al.* (2015) Roller compactor: the effect of mechanical properties of primary particles. *Int. J. Pharm.* 496, 124–136

60 Li, H. *et al.* (2015) Examining drug hydrophobicity in continuous wet granulation within a twin screw extruder. *Int. J. Pharm.* 496, 3–11

61 Maniruzzaman, M. *et al.* (2015) One-step continuous extrusion process for the manufacturing of solid dispersions. *Int. J. Pharm.* 496, 42–51

62 Maniruzzaman, M. *et al.* (2015) Continuous twin-screw granulation for enhancing the dissolution of poorly water soluble drug. *Int. J. Pharm.* 496, 52–62

63 Sayin, R. *et al.* (2015) Investigation of an 11 mm diameter twin screw granulator: screw element performance and in-line monitoring via image analysis. *Int. J. Pharm.* 496, 24–32

64 Meier, R. *et al.* (2015) Simplified formulations with high drug loads for continuous twin-screw granulation. *Int. J. Pharm.* 496, 12–23

65 Kelly, A.L. *et al.* (2015) A novel transflectance near infrared spectroscopy technique for monitoring hot melt extrusion. *Int. J. Pharm.* 496, 117–123

66 Patil, H. *et al.* (2015) Formulation and development of pH-independent/dependent sustained release matrix tablets of ondansetron HCl by a continuous twin-screw melt granulation process. *Int. J. Pharm.* 496, 33–41

67 Crowley, M.M. *et al.* (2007) Pharmaceutical applications of hot-melt extrusion: part I. *Drug Dev. Ind. Pharm.* 33, 909–926[DE15]

68 Dalziel, G. *et al.* (2013) Assessment of granulation technologies for an API with poor physical properties. *Drug Dev. Ind. Pharm.* 39, 985–95

69 Todd, D.B., ed. (1998) *Plastics Compounding Equipment and Processing*, Publisher[DE16]

70 Wagner, J. and Vlachopolous, J., eds (2001) *The SPE Guide on Extrusion Technology and Troubleshooting*, Publisher[DE17]

71 Nowak, S. (2008) Feeders in milling and micronization of pharmaceutical powders. *Chem. Info[DE18]*

72 Islam, M.T. *et al.* (2015) Implementation of transmission NIR as a PAT tool for monitoring drug transformation during HME processing. *Eur. J. Pharm. Biopharm.* 96, 106–116

73 Paulsen, K. *et al.* (2013) Investigating process parameter mechanism for successful scale-up of a hot-melt extrusion process. *ThermoScientific* 2013, LR-71

74 Anon. (XXXX[DE19]) *Analytical Tools and Techniques in Hot Melt Extrusion*, Foster Delivery Science

75 Ozen, I. *et al.* (2012) Modification of surface properties of polypropylene films by blending with poly(ethylene-b-ethylene oxide) and its application. *Polym. Bull.* 68, 575–595

76 Berzin, F. *et al.* (2006) Evolution of the peroxide-induced degradation of polypropylene along a twin-screw extruder: experimental data and theoretical predictions. *J. Appl. Polym. Sci.* 99, 2082–2090

77 Carneiro, O.S. *et al.* (2000) Experimental and theoretical study of twin-screw extrusion of polypropylene. *J. Appl. Polym. Sci.* 78, 1419–1430

78 Doufas, A.K. *et al.* (2007) Experimental studies of polypropylene extrusion instability. In *Proceedings of the Annual Technical Conference* (eds[DE20]), pp. 415–419, Society of Plastic Engineers

79 Damir, E. *et al.* (2013) Rational development of solid dispersions via hot-melt extrusion using screening, material characterization, and numeric simulation tools. *J. Pharm. Sci.* 102, 2297–2310

80 Dalziel, G. *et al.* (2013) Assessment of granulation technologies for an API with poor physical properties. *Drug Dev. Ind. Pharm.* 39, 985–995

81 US FDA Center for Drug Evaluation and Research (2003) *Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*, FDA

82 US FDA Center for Drug Evaluation and Research (2014) *Current Good Manufacturing Practice for Manufacturing, Processing, Packing, or Holding of Drugs*, FDA

83 Anon. (2005) *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Risk Management Q9*, ICH

84 Anon. (20080 *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Pharmaceutical Quality Systems Q10*, ICH

85 Anon. (2012) *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Development and Manufacture of Drug Substances Q11*, ICH

86 US FDA Center for Drug Evaluation and Research (2004) *Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, FDA

87 Anon. (2007) *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Pharmaceutical Development Annex to Q8*, ICH

88 Maniruzzaman, M. *et al.*, (2016) Development and optimization of ketoconazole oral strips by means of continuous hot-melt extrusion processing. *J. Pharm. Pharmacol.* 68, 890–900

89 Wold, S. *et al.* (2006) The chemometric analysis of point and dynamic data in pharmaceutical and biotech production (PAT) — some objectives and approaches. *Chem. Intell. Lab. Syst.* 84, 159–163

90 Saerens, L. *et al.* (2010) Raman spectroscopy for the in-line polymer-drug quantification and solid state characterization during a pharmaceutical hot-melt extrusion process. *Eur. J. Pharm. Biopharm.* 77, 158–163

Figure 1. A continuous manufacturing diagram involving hot melt-extrusion (HME) with monitoring system and process controls. Abbreviation: API, active pharmaceutical ingredient.

Figure 2. Title[DE21]. Composite image of a **(a)** sagittal cut and **(b)** transverse cut of a 130% implant. The inner part of the implant is shown in red (active pharmaceutical ingredient; API) and the membrane is shown in green (EVA[DE22]). **(c,d)** Spectrum resolved by MCR-ALS (in red) and the pure API spectrum (blue). An increment has been added to the resolved spectrum for better visibility. The correlation coefficient between the reference and resolved

spectra was 98.97% (c) and 98.29% (d). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) [44].

Figure 3[DE23]. Title[DE24]. (a) Scanning electron micrographs of 15% tramadol hydrochloride in glyceryl behenate granules prepared by (i) continuous twin screw granulation and (ii) melt mixing and grinding. (Bi) Continuous twin-screw granulation temperatures encountered by the granulation while traversing the extruder barrel. (bii) Particle size distributions of granules produced at each temperature profile [53].

Figure [DE25]**4.** Instrumentation set-up for twin-screw granulation of ibuprofen and characterizations comprising a Eurolab 16 extruder and the granulating liquid feeding pump [62].

Figure 5. [DE26]Process parameter chart during a scale-up via hot melt-extrusion (HME) [72].

Figure 6. [DE27]Process parameter information using a process analytical technology (PAT) approach. Abbreviation: ASTM, American Society for Testing and Materials.

Table 1. Levels of the classification of PAT applications

Level	Description[a]
PAT Level I	Determination of the concentration and other properties of component from the spectrum
PAT Level II	Raw material quality checks and the classification from spectral data
PAT Level III	Batch process monitoring by means of the multivariate measurement
PAT Level IV	Using the batch monitoring data and process information to predict the quality of the product
PAT Level V	Feedback control of the process to maintain the quality of the product

[a]From [89,90].

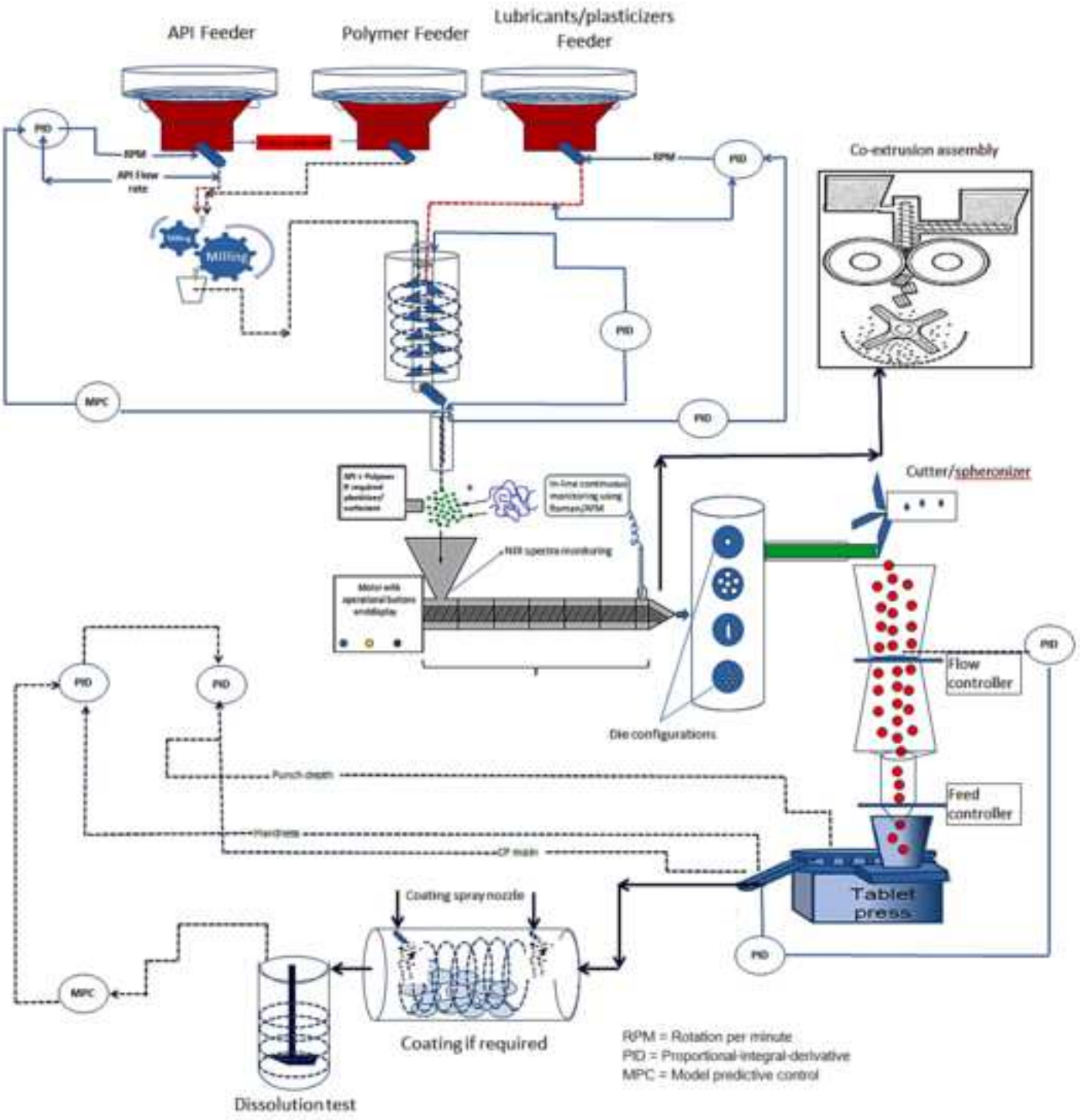
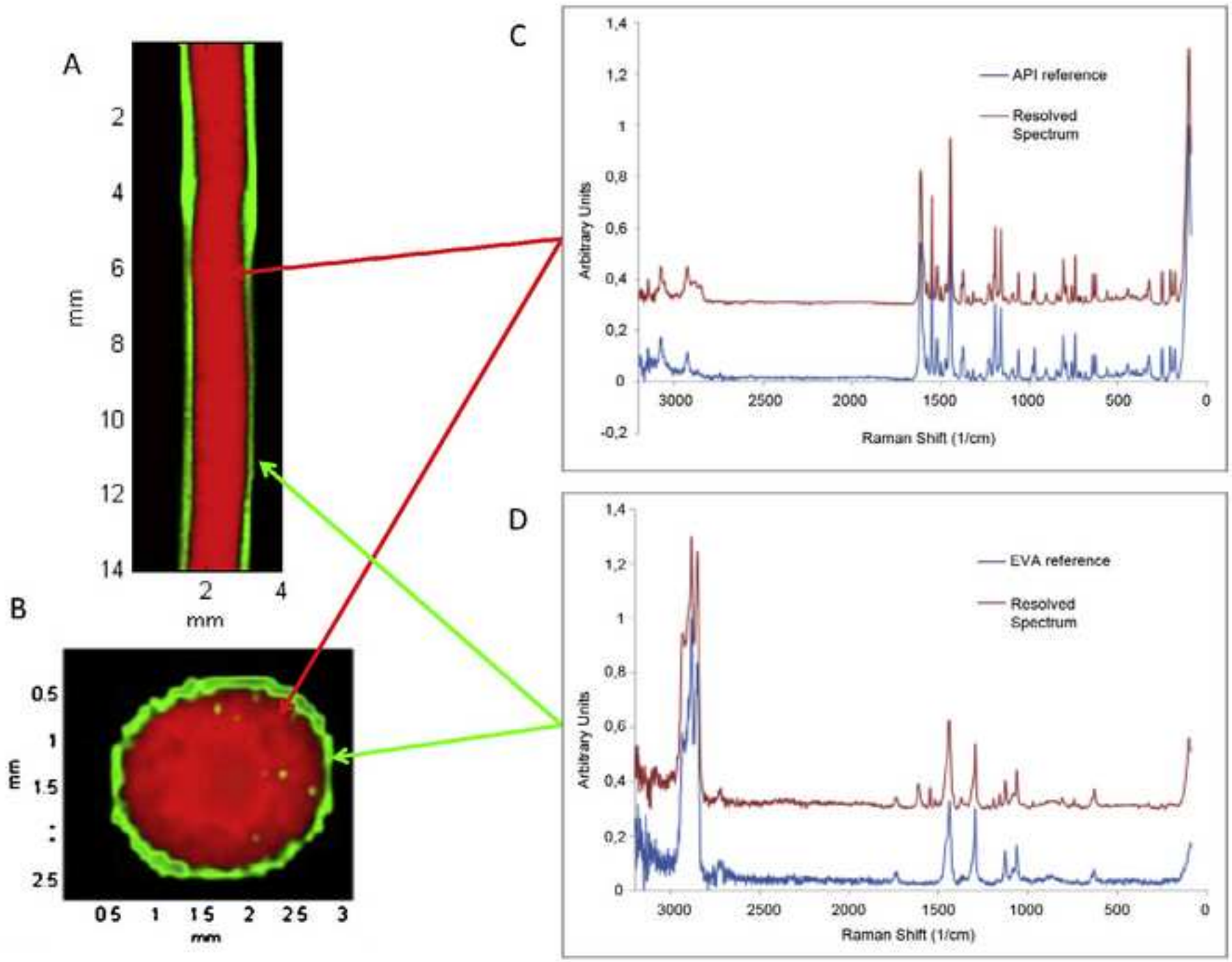


Figure 2


A
2
4
6
8
10
12
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mm
2
4
mm
B
0.5
1
1.5
2.5
mm
0.5
1
1.5
2
2.5
3
mm
C
1,4
1,2
1
0,8
0,6
0,4
0,2
0
-0,2
Arbitrary Units
API reference
Resolved Spectrum
3000
2500
2000
1500
1000
500
0
Raman Shift (1/cm)
D
1,4
1,2
1
0,8
0,6
0,4
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Arbitrary Units
EVA reference
Resolved Spectrum
3000
2500
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1500
1000
500
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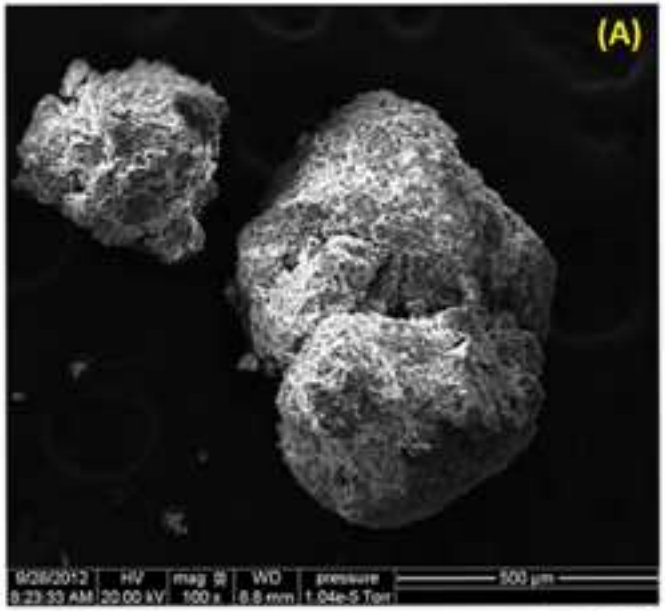
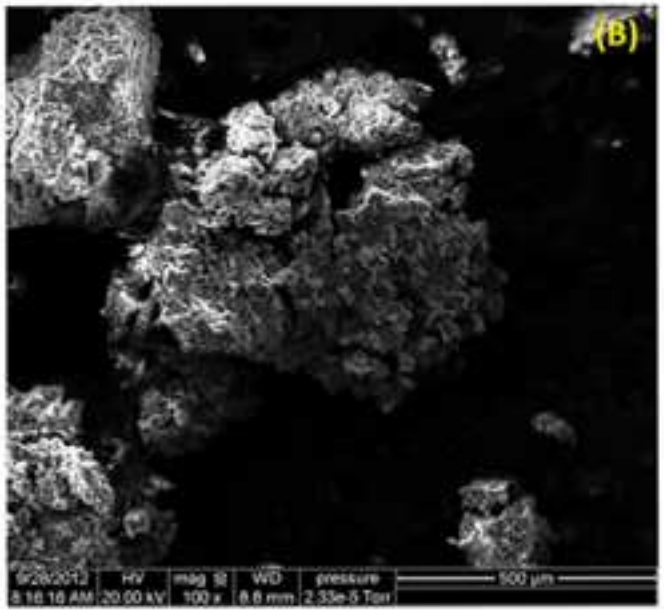
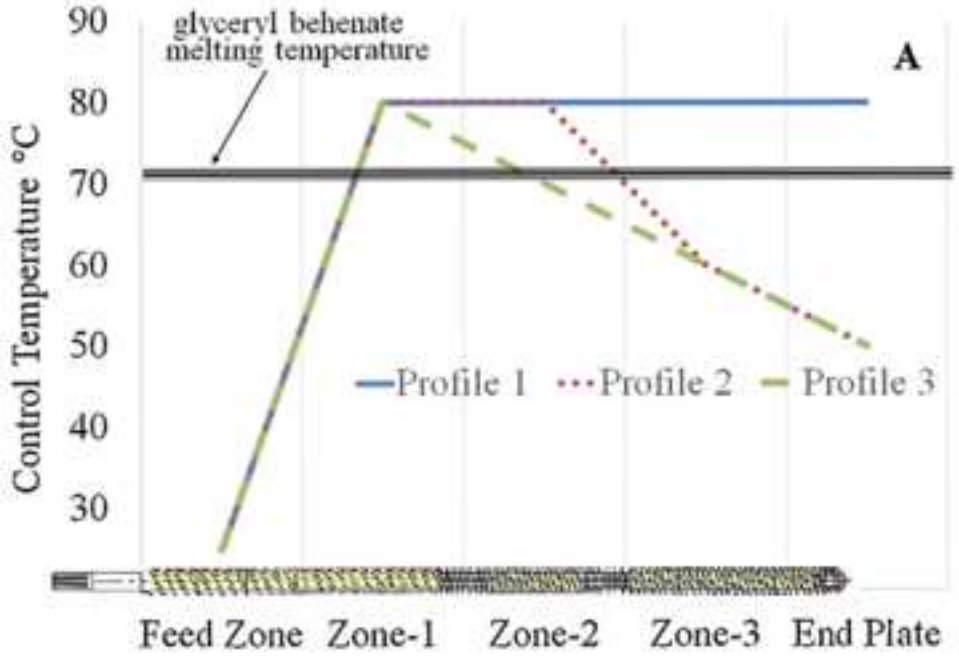
Raman Shift (1/cm)

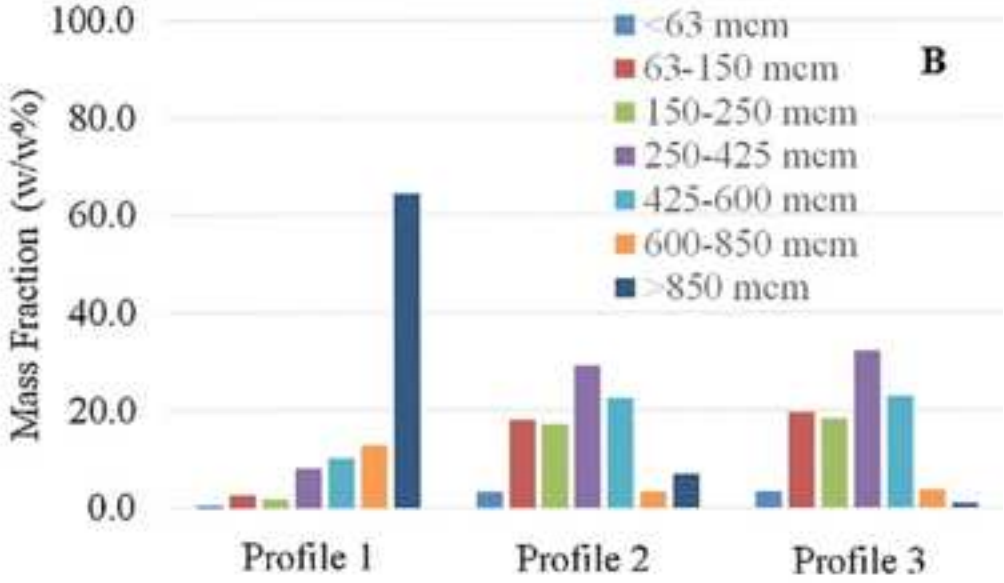
Figure 3


(A)


(B)

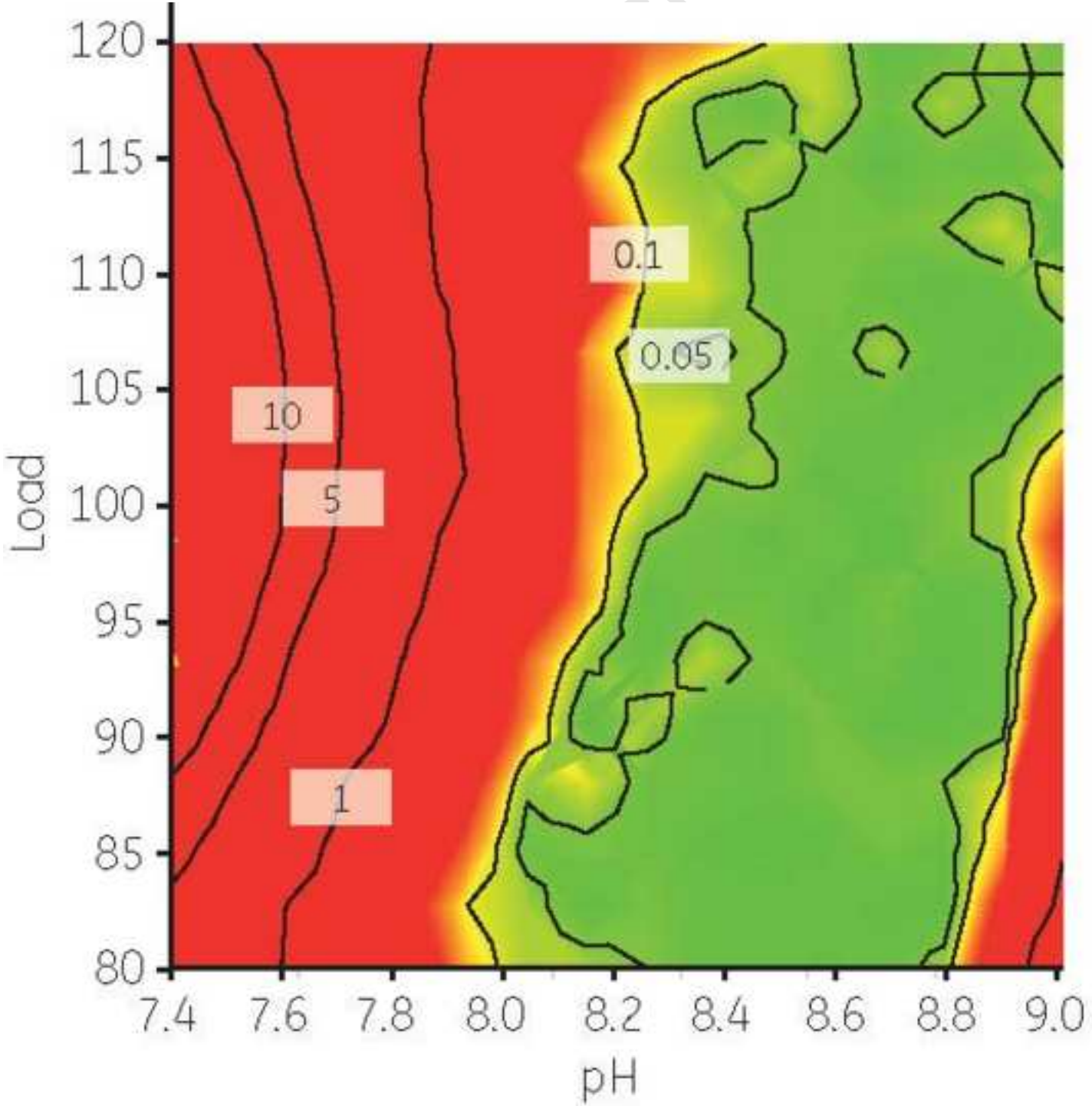
(i)


glyceryl behenate
melting temperature
A
Control Temperature °C
90
80
70
60
50
40
30
Profile 1
Profile 2
Profile 3
Feed Zone
Zone-1
Zone-2
Zone-3
End Plate


B
Mass Fraction (w/w%)
100.0
80.0
60.0
40.0
20.0
0.0
<63 mcm
63-150 mcm
150-250 mcm
250-425 mcm
425-600 mcm
600-850 mcm
>850 mcm
Profile 1
Profile 2
Profile 3

(ii)

Figure 4


120
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Load
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8.6
8.8
9.0
pH
0.1
0.05
10
5
1

Figure 5

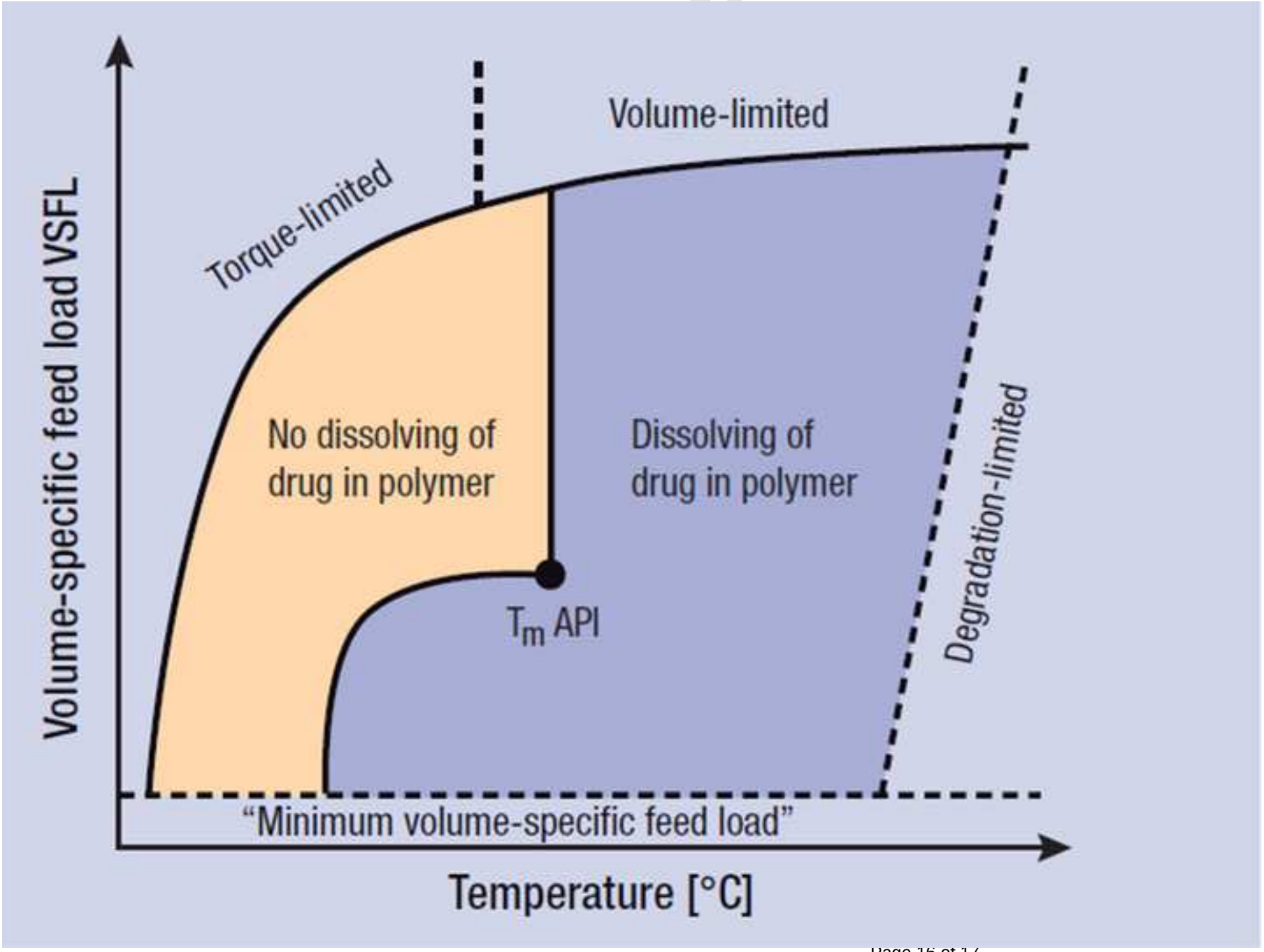
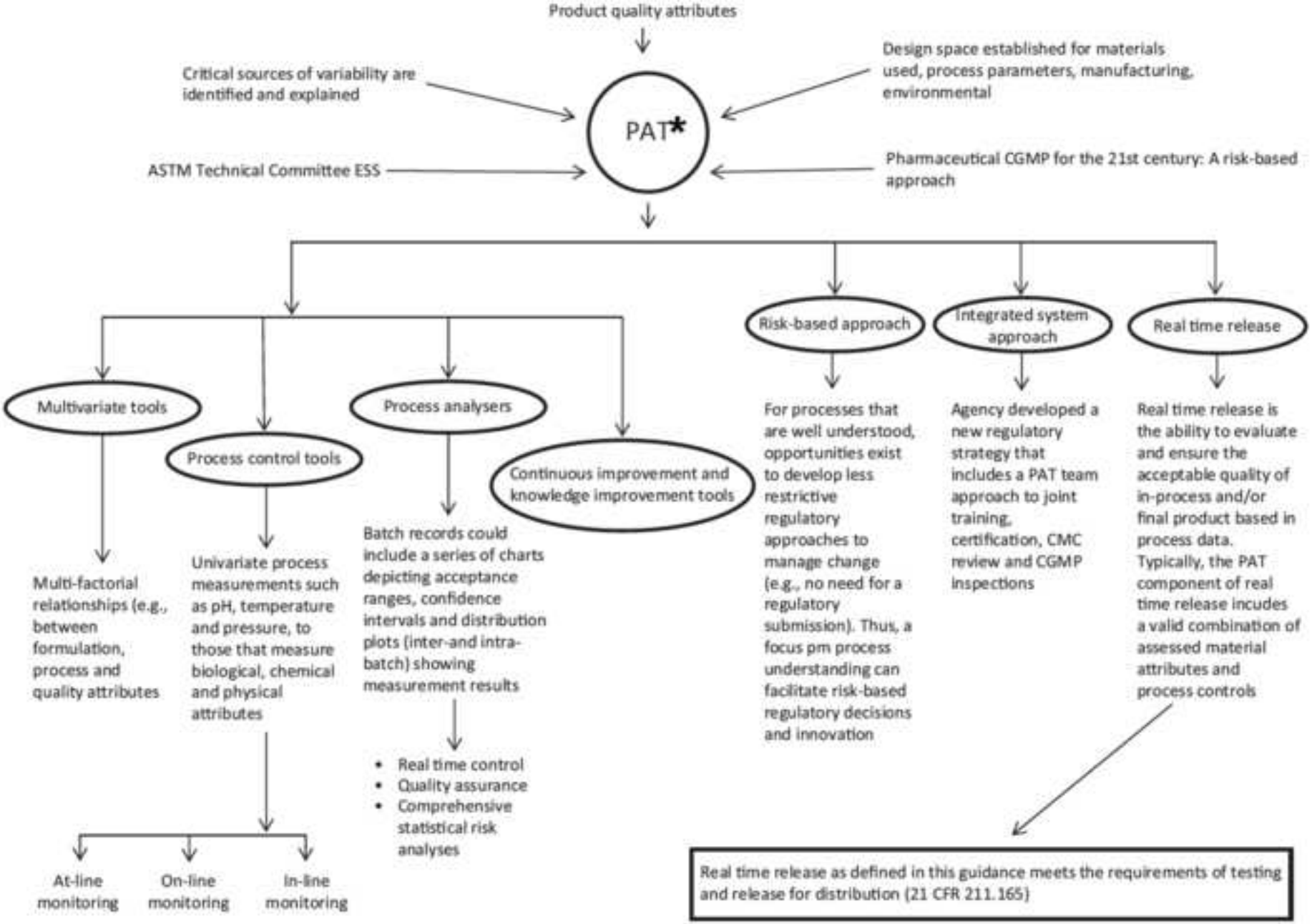

Volume-specific feed load VSFL
Volume-limited
Torque-limited
No dissolving of drug in polymer
Dissolving of drug in polymer
T_m API
Degradation-limited
"Minimum volume-specific feed load"
Temperature [°C]

Figure 6



* PAT = Process analytical technology